REMARKS

Claims 2-11, 13-15, and 35 have been cancelled. Claim 1 has been amended as discussed below. Claim 20 has been amended to correct a clerical error. New claim 37 is added. Claims 1, 12, 16-34, and 36-37 are now pending in this application. Claims 16, 18, and 19 are withdrawn from consideration. Support for the amendments is found in the existing claims and the specification as discussed below. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Telephone interview

Applicant gratefully acknowledges the impromptu telephonic interview with Examiner Li on May 11, 2006 summarized herein. As a result of that conversation, additional amendments have been made to claim 1 and additional arguments are presented for grounds of rejection based upon the primary references Banai, et al., Pu, et al., and Fasol, et al. relative to the After Final Response of January 30, 2006. These arguments are presented below. The remaining rejections over art are believed to be overcome by submission of Declarations under In re Katz and 37 C.F.R. § 1.131 as discussed in the Amendment after Final of January 30, 2006 and repeated below.

Election/Restrictions

With this amendment, Applicants have amended claim 1 to be generic to the species identified as SEQ ID NOS: 1, 3, 4, AND 6. These species are now listed in new claim 37.

Priority

Claim 1 has been amended so that it is fully supported by the earliest priority application. The listing of specific SEQ ID NOS has been deleted from claim 1 and is now added as dependent claim 37. In addition, claim 1 has been amended to recite that injection of FGF-1 is into the ischemic region of the myocardium. Support for this amendment is found in parent application no. 09/358,780 at page 17, lines 28-29 and page 22, line 26. Support in provisional application no. 60/093,962 is found on page 18, lines 26-28 and page 23, line 26. General support for recombinant hFGF is found in the specification at pages 9, line 1 to page 17, line 7 (09/358,780) and at page 9, line 9 to page 18, line 5 of provisional application 60/093,962. Neoangiogenesis is shown at Figures 3A & B as discussed on page 19, line 26 to page 20, line 10

of U.S. Application No. 09/358,780 and on page 20, line 26 to page 21, line 10 in provisional application 60/093,962 and Figures 4-7 discussed in U.S. Application No. 09/358,780 on page 21, line 21 to page 24, line 22 and in provisional application 60/093,962 at page 22, line 21 to page 25, line 25. Support for the recitation of "whereby at least one clinical index of cardiac function is enhanced in the human subject" is found in the present specification at page 39, paragraph 0155, in U.S. Application No. 09/358,780 at page 24, lines 13-19, and in the provisional application 60/093,962 at page 25, lines 15-22.

It is respectfully submitted that claim 1 as amended is completely supported by application No. 09/358,780, filed July 22, 1999 and the corresponding provisional application 60/093,962, filed July 24, 1998.

Declaration

The Office Action states that the Declaration of Dr. Stegmann filed on August 25, 2005 is insufficient to overcome the rejection over Schumacher, et al. because of the amendment to claim 1 filed with the paper of August 2005.

With the present paper, claim 1 has been amended so that claim 1 is fully supported by application No. 09/358,780, filed July 22, 1999 and the corresponding provisional application 60/093,962, filed July 24, 1998. The amendment filed August 2005 included a Declaration under in Re Katz to overcome the rejection over Schumacher, et al. and a Declaration under 37 C.F.R. § 1.131 to overcome Htun, et al. Copies are resubmitted here for convenience. See response to grounds of rejection below.

Applicants respectfully request reconsideration of the previously submitted Declarations in view of Applicant's amendment of claim 1 so that it is now supported by the July 24, 1998 disclosure.

Rejection under 35 U.S.C. § 103(a)

Claims 1-15, 17, 20-34, and 36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Schumacher, et al. (Circulation, Feb, 1998, Vol. 97, pp. 645-650) for claims 1, 3-11, 13-15, 20-22, 33, and 36, Jaye, et al. (U.S. Patent No. 5,571,790A) and Fasol. et al. (J. Thorac. Cardiovasc. Surg. 1994, Vol. 107, pp 1432-1439).

Applicant again presents the attached Declaration under In re Katz to overcome this ground of rejection in view of the present claim amendments. The present claim 1 is supported

by Applicant's provisional application 60/093,962, filed July 24, 1998 as discussed above. Accordingly, Schumacher, et al. is no longer a reference under 35 U.S.C. § 102(b).

As presented with the August 2005 Amendment, Applicant is one of the co-authors of the cited reference. As set forth in the attached Declaration, the three co-authors worked under the direct guidance and direction of Applicant and did not contribute to the inventive concept of the claimed invention. Accordingly, the claimed invention was not described in a printed publication before the invention thereof by Applicant.

In view of the attached Katz Declaration, Applicant's amendment of claim 1, and the Remarks above, reconsideration and withdrawal of this ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 12 and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Pu, et al. (Circulation 1993, Vol. 88, No. 1, pages 208-215), Linemeyer (U.S. Patent No. 5,401,832) and Kordyum, et al. (U.S. Patent No. 6,773,899).

This ground of rejection is overcome in part by Applicant's amendment of claim 1 and in part by the additional arguments presented below. Claim 1 has been amended to recite that the recombinant hFGF is injected "into the ischemic region of the myocardium". The disclosure of Pu, et al. relates to revascularization of an ischemic limb. There is nothing in Pu, et al. that would teach or suggest to one of ordinary skill in the art that hFGF could be injected into an ischemic region of myocardium to induce local neoangiogenesis.

Furthermore, the disclosure of Pu, et al. uses an animal model (New Zealand white rabbits) while the present claims are directed to human subjects and have been amended to recite "whereby at least one clinical index of cardiac function is enhanced in the human subject". Support for the amendment is found in the present specification at page 39, paragraph 0155 and in the provisional application at page 25, lines 15-22. Pu, et al. do not teach improvement in cardiac function in human patients. Pu, et al. are concerned with lower-extremity ischemia, not cardiac ischemia. Pu, et al. do not teach the limitations of the present claims.

Furthermore, as discussed in the present specification and parent applications, the clinical effects of FGF in human patients were surprising in view of the frequent incidence of restenosis in the patients that were treated during the study. Improved vascularization as evidenced by

enhanced ejection fraction was evident 3 years after the procedure (paragraph 0155 of the present specification and page 25, lines 10-15 of the provisional application 60/093,962). These results could not have been predicted from the work reported by Pu, et al. on lower-extremity ischemia in rabbits.

Furthermore, the role of FGF was by no means clear at the time of the claimed invention. As discussed by Pu, et al. on page 213, col. 2, first paragraph, Banai, et al. (discussed further below) were unable to demonstrate benefit from delivery of FGF to ischemic myocardium from an epicardial sponge. Accordingly, there was no reasonable expectation of success that a human subject could enjoy increased cardiac function after injection of FGF into an ischemic region of a myocardium based upon the disclosure of Pu, et al. on ischemic limbs in rabbits, especially in view of the failure of Banai, et al. to demonstrate angiogenesis when FGF was administered to ischemic myocardium in dogs. Furthermore, it was unexpected that the improved cardiac function could be observed 3 years after the procedure, especially in view of the uncertainty as to the physiological role of FGF as discussed by Pu, et al. with respect to Banai, et al.

The deficiencies above are not corrected by either of Linemeyer or Kordyum, et al. Linemeyer, et al. merely disclose that FGF-1 may be used to promote revascularization of a grafted blood vessel. Linemeyer, et al. do not teach injection of FGF-1 into the myocardium.

Kordyum, et al. is not prior art to present claim 1, amended as discussed above, as the earliest possible date for the Kordyum, et al. reference is Aug. 15, 2000 based upon a provisional filing. The present claim 1 has priority from July 24, 1998. Furthermore, Kordyum, et al. also do not teach injection into the myocardium.

In view of Applicant's amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 12, 17 and 36 are rejected as being unpatentable over Banai, et al. (Cir. Res. 1991, Vol. 69, No. 1, pp 76-85), Linemeyer (U.S. Patent No. 5,401,832) and Kordyum, et al. (U.S. Patent No. 6,773,899).

Banai, et al. do not teach the invention claimed as Banai, et al. do not teach injection of FGF into the ischemic region of the myocardium. Rather Banai, et al. teach introduction of FGF using an epicardial sponge (see Abstract). One of ordinary skill in the art would not be motivated

to directly inject FGF into a myocardium in view of Banai, et al. as Banai, et al. neither teaches nor suggests direct injection.

Furthermore, Banai, et al. were unsuccessful in achieving angiogenesis by administration of FGF. The following are quotes taken from their Discussion on page 84, col. 1:

"Unfortunately, in our preparation, no arteriographic or microscopic evidence of blood vessel formation was found after 4 weeks."

"Thus, the acidic-FGF-treated sponges failed to exert significant angiogenic properties in the canine mediastinum in this model. The primary aim of our study was to assess the angiogenic potential of acidic FGF on the myocardium, and we would be reluctant to extrapolate our finding to the therapy of acute myocardial infarction."

"Thus, no conclusions can be drawn from our observation regarding the potential role of acidic FGF in the treatment of myocardial infarction. However, our results do suggest that careful studies need to be performed before it can be concluded that acidic FGF has either a salutary or a detrimental effect in this situation."

"Although SMC proliferation is an integral part of an angiogenic response, the creation of myocardial vessels undoubtedly requires a complex series of events that is not mimicked by simple exposure of ischemic myocardium to acidic FGF."

Accordingly, Banai, et al. would not motivate one of ordinary skill in the art to administer FGF to an ischemic region and, if anything, teach away from the claimed invention. Banai, et al. administrate the FGF differently (by sponge) and observe a different effect than Applicant, i.e. no angiogenesis. This provides evidence that the present claims are non-obvious over Banai, et al. One of ordinary skill in the art would not be motivated to practice Applicant's invention because Banai, et al. do not teach direct injection and do not teach angiogenesis.

Furthermore, Banai, et al. do not teach human subjects and do not teach "whereby at least one clinical index of cardiac function is enhanced in the human subject" as now recited in

amended claim 1. Support for the amendment is found in the present specification at page 39, paragraph 0155 and in the provisional application at page 25, lines 15-22. Neither angiogenesis nor improved cardiac function are taught by Banai, et al.

As discussed in the present specification and parent applications, the clinical effects of FGF were surprising in view of the frequent incidence of restenosis in the patients that were treated during the study. Also, the improved vascularization as evidenced by enhanced ejection fraction was evident 3 years after the procedure (paragraph 0155 of the present specification and page 25, lines 10-15 of the provisional application 60/093,962).

Furthermore, the role of FGF was by no means clear at the time of the claimed invention. On page 83, col. 1, last paragraph, Banai, et al. state that "Although acidic and basic FGFs have been identified in the heart, their physiological role has not been elucidated". Accordingly, the physiological role of FGF had not been well characterized, at least a the time of the Banai, et al. reference.

The deficiencies above are not corrected by either of Linemeyer or Kordyum, et al. for the reasons discussed above. As discussed above, Linemeyer, et al. do not teach injection of FGF-1 into the myocardium. Kordyum, et al. do not teach injection into the myocardium and is not prior art to the present claims.

Kordyum, et al. is not prior art to present claim 1, amended as discussed above, as the earliest possible date for the Kordyum, et al. reference is Aug. 15, 2000 based upon a provisional filing. The present claim 1 has priority from July 24, 1998. Furthermore, Kordyum, et al. also do not teach injection into the myocardium.

In view of Applicant's amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 12, 17, and 36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Htun, et al. (J. Mol. Cell. Cardiol April 1998, Vol. 30, pp 867-877), Linemeyer, et al. (U.S. Patent No. 5,401,832A), and Kordyum et al. (U.S. Patent No. 6,773,899B2).

In order to overcome this ground of rejection, Applicant respectfully resubmits the Declaration under 37 C.F.R. § 1.131 previously submitted with the Amendment of August 2005. This Declaration was originally submitted in parent Application No. 09/358,780. The

Declaration established that Applicant had completed his invention before January 9, 1997 which is before the date of the Htun, et al. reference, i.e. April 1998. In view of Applicant's amendments, claim 1 is now fully supported by Applicant's provisional application filed July 24, 1998. Accordingly, Applicant respectfully requests reconsideration of the Declaration under 37 C.F.R. § 1.131 in view of the amendments to claim 1.

In view of Applicant's amendments and the submitted Declaration under 37 C.F.R. § 1.131, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 12, 17, 23-27, 34, and 36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fasol, et al. (J. Thorac Cardiovasc. Surg. 1994, Vol. 107, pp.1432-1439), Linemeyer (U.S. Patent No. 5,401,832) and Kordyum, et al. (U.S. Patent No. 6,773,899).

Fasol, et al. differ from the presently claimed invention in that Fasol, et al. teaches a fibrin glue implant in non-ischemic tissue, not injection into an ischemic region of the myocardium. Fasol, et al. teach implantation between the aorta and the myocardium of the left ventricle (see last two lines of page 1), not injection directly into the myocardium. As Fasol, et al. neither teach nor suggest injection into the myocardium, one of ordinary skill in the art would not be motivated to inject FGF into the myocardium in view of Fasol, et al.

Also, Fasol, et al. do not teach treatment of ischemic tissue as claimed. Fasol, et al. "did not choose the model of induced angiogenesis in ischemic myocardial tissue beds to avoid possible angiogenic effects of endogenous biochemical agents released by such ischemia-injured tissue" (page 9 of 14, first full paragraph). In contrast, claim 1 is drawn to injection "into the ischemic region of the myocardium". Furthermore, present claim 1 has been amended to recite "whereby at least one clinical index of cardiac function is enhanced in the human subject". Support for the amendment is found in the present specification at page 39, paragraph 0155 and in the provisional application at page 25, lines 15-22). This aspect is not taught by Fasol, et al. as Fasol, et al. do not teach human subjects and do not teach treatment of ischemic tissue.

As discussed in the present specification and parent applications, the improved cardiac function 3 years after the injection of FGF were surprising in view of the frequent incidence of restenosis in the patient sample pool that were treated during the study. The improved

vascularization as evidenced by enhanced ejection fraction was evident 3 years after the procedure (paragraph 0155 of the present specification and page 25, lines 10-15 of the provisional application 60/093,962). These results could not have been predicted from the work of Fasol, et al. because Fasol, et al did not use human subjects, did not teach injection into an ischemic region of the myocardium, did not use a sample pool with a frequent incidence of restenosis and did not teach an improvement of cardiac function 3 years out from the time of treatment. Accordingly, the claimed invention is non-obvious in view of Fasol, et al.

Furthermore, the role of FGF was by no means clear at the time of the claimed invention as discussed above in the response to the rejections based upon Pu, et al. and Banai, et al.. There was no reasonable expectation of success that a human subject could enjoy increased cardiac function after injection of FGF into an ischemic region of a myocardium. Furthermore, it was unexpected that the improved cardiac function could be observed 3 years after the procedure, especially in view of the uncertainty as to the physiological role of FGF as discussed above.

The deficiencies above are not corrected by either of Linemeyer or Kordyum, et al. Linemeyer, et al. merely disclose that FGF-1 may be used to promote revascularization of a grafted blood vessel. Linemeyer, et al. do not teach injection of FGF-1 into the myocardium.

Kordyum, et al. is not prior art to present claim 1, amended as discussed above, as the earliest possible date for the Kordyum, et al. reference is Aug. 15, 2000 based upon a provisional filing. The present claim 1 has priority from July 24, 1998. Furthermore, Kordyum, et al. also do not teach injection into the myocardium.

In view of Applicant's amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: May 15, 2006

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SUMMARY OF INTERVIEW

Exhibits and/or Demonstrations

no

Identification of Claims Discussed

all

Identification of Prior Art Discussed

none specifically

Proposed Amendments

as discussed below

Principal Arguments and Other Matters

Examiner Li was contacted to discuss a possible interview to discuss claim amendments in addition to the amendments and arguments presented with the After Final response of January 30, 2006 which was not entered. Examiner Li had not reviewed the application at the time of the phone call and did not think that it would be possible to have an interview before the May 15th final deadline because of the short deadline and the limited availability of her Supervisor during that time period. However, she did provide helpful remarks during a discussion of issues in the application.

To summarize the Examiner's position, Examiner Li maintained that the function of FGF was known and Applicant was using FGF for its known function. Applicants' representative mentioned that none of the references cited taught injection into the myocardium and that the specification presented data from extensive human trials. Examiner Li did not think that it would make a patentable difference where you inject or how the FGF is delivered, but suggested that we amend the claims to recite some unique step or observation in view of the data based upon human subjects which would not be found in the cited references which are based on animal models.

Results of Interview

With this amendment, claim 1 has been amended to recite that administration is to a human subject and "whereby at least one clinical index of cardiac function is enhanced in the human subject." This result is not taught by the cited references which are directed to animal

models and do not teach any improved function for the treated subjects. Applicant believes that claim 1 is entitled to the priority of the earliest filed application, U.S. Provisional Application No. 60/093,962, filed July 24, 1998. Support in the provisional filing is discussed below. Additional arguments for references that predate the July 24, 1998 filing are presented below.